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Research Article

CONTROLLED RELEASE IN SITU FORMING GATIFLOXACIN HCl HYDROGEL FOR OPHTHALMIC DRUG DELIVERY

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ABSTRACT
Recently, controlled drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. In situ hydrogels are instilled as drops into the eye and undergoes a sol to gel transition in the cul-de-sac, improved ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration. The purpose of the present work was to develop an ophthalmic drug delivery system using the three different gelling agents with different mechanisms for in situ gelation of Gatifloxacin hydrochloride, a fluoroquinolone antibiotic. Polyox – a pH sensitive gelling agent and sodium alginate is an ion sensitive gelling agent and Poloxamer – a temperature sensitive gelling agent were employed for the formation of in situ hydrogel along with HPMC K4M as viscofying agent. The promising formulations were evaluated for pH, drug content, in vitro gelation, in vitro drug release, in vivo drug release, ocular irritation.

Keywords: controlled release, In situ-forming hydrogel, Gatifloxacin Hydrochloride, Polyox, poloxamer.

INTRODUCTION

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. Amongst the extensive research has been carried in designing of polymeric drug delivery systems. The development of in situ gel systems has received considerable attention over the past few years. In the past few years, increasing number of in situ gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported.[1]

In situ gel formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes, which can be inconvenient or oral route, which can result in unacceptably low bioavailability and passes the hepatic first-pass metabolism, in particular of proteins and peptides. [2] This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with mucosa, that problems generally encountered in semi- solid dosage forms. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. [3] Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems. [4]

Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result into poor bioavailability of drug in the ocular cavity. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration.[5] Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss. [6]

Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ophthalmic drug delivery; one of the ways to do so is by addition of polymers of various grades, development of in situ gel or colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention.[7]

Ophthalmic drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientist.[8] the landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fueling the demand for novel drug delivery. The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the site of action for the sufficient period of time to elicit a response. The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity, but still with a minimum risk of ocular complications. A major problem of ophthalmic drug delivery is not the lack of efficient drugs but the attainment of their optimal concentration at the site of their optimal concentration at the site of action. The emergence of new and innovative means

for improving therapeutic efficacy suggests that a greater choice of dosage forms will be provided to physicians and patients in the next decade. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss.[9]

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains. They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore, the high water content of the materials contributes to their biocompatibility.[10] Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration.[11]These are polymers endowed with an ability to swell in water or aqueous solvents and induce a liquid–gel transition.[12] Currently, two groups of hydrogels are distinguished, namely preformed and in situ forming gels. Preformed hydrogels can be defined as simple viscous solutions which do not undergo any modifications after administration. The use of preformed hydrogels still has drawbacks that can limit their interest for ophthalmic drug delivery or as tear substitutes. They do not allow accurate and reproducible administration of quantities of drugs and, after administration; they often produce blurred vision, crusting of eyelids, and lachrymation. Thus in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three methods have been employed to cause phase transition on the surface: change in temperature, pH, and electrolyte composition.[13]

Increase in solution viscosity by using polymers improves retention of product on the corneal surface. More recently, the approach to improve precorneal retention is based on the use of mucoadhesive polymers. The principle for use of bioadhesive vehicles relies on their ability to interact with the mucin-coating layer present at the eye surface. The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics. It is generally well accepted that the instillation of a formulation should influence tear behaviour as little as possible. Because tears gave a pseudoplastic behavior, pseudoplastic vehicles would be more suitable as compare to Newtonian formulations, which have a constant viscosity independent of the shear rate, whereas pseudoplastic solution exhibit decreased viscosity with increasing shear rate, thereby offering lowered viscosity during blinking and stability of the tear film during fixation.[14-15]

Drug release from hydrogels

As discussed in the previous sections, hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water (N 90 wt. %). Therefore, the molecule release mechanisms from hydrogels are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate limiting step for controlled release and are therefore categorized as diffusion, swelling & chemically controlled mechanism.

MATERIALS AND METHODS

Gatifloxacin Hydrochloride was obtained as gift sample from Dana pharmaceuticals Pvt. Ltd, Ambarnath, India. Hydroxy Propyl Methyl Cellulose (K4M), Polyox, Sodium alginate were Procured from Colorcon Asia Pvt.Ltd. Goa, India. Acetonitrile were purchased from SD Fine chemicals, Mumbai, India. All other reagents and solvent used were of analytical grade. Cellophane membrane and distilled water were the other materials used.

Instruments used

UV-spectrophotometer (shimadzu Lab.), Brookfield DV Rheometer (Brookfield Engineering Laboratories), Magnetic stirrer Autoclave, were the instruments used for this study.

Method

Standard calibration curve[16]

Accurately weighed 100 mg Gatifloxacin Hydrochloride was dissolved in 0.1N HCl in 100 ml calibrated flask to get the stock solution. From this stock solution aliquots of 2, 4, 8, 10, 12, & 14 ml were withdrawn and further diluted to 100 ml with 0.02N HCl to obtain a suitable concentrations range. The absorbance of the solutions was measured at 280 nm by using UV spectrophotometer. A graph of Concentration vs. Absorbance was plotted.

Table 1: Formulation of Gatiifloxacin Hydrochloride in situ hydrogel

SR NO	Ingredient	MF1	MF2	MF3
1	Gatifloxacin HCl	0.5% w/v	0.5% w/v	0.5% w/v
2	Polyox	1.2% w/v	---	---
3	Sodium alginate	---	1% w/v	---
4	Poloxamer	---	---	18% w/v
5	HPMC K4M	0.5% w/v	0.5% w/v	0.5% w/v
6	Acetate buffer	---	---	100ml
7	Citrophosphate buffer	100ml	---	---
8	Distilled water	---	100ml	---
9	Sodium hydroxide	---	QS	---
10	Hydrochloride acid	---	QS	---

Evaluation

A. Appearance

Clarity is one of the most important characteristic features of ophthalmic preparations. All developed formulations were evaluated for clarity by visual observation against a black and white background.

B. pH

pH is one of the most important parameter involved in the ophthalmic formulation. The two areas of critical importance are the effect of pH on solubility and stability. The pH of ophthalmic formulation should be such that the formulation will be stable at that pH and at the same time there would be no irritation to the patient upon administration of the formulation. Ophthalmic formulations should have pH range in between 5 to 7.4. The developed formulations were evaluated for pH by using Elico India Systronics digital pH meter.

C. Drug Content

Uniform distribution of active ingredient is important to achieve dose uniformity. The drug content was determined by diluting 1 ml of the formulation to 50 ml with phosphate buffer solution pH 7.4. Aliquot of 5 ml was withdrawn and further diluted to 50 ml with PBS. Gatifloxacin hydrochloride concentration was then determined at 290 nm by using UV-Vis spectrophotometer.

D. In vitro Gelation Studies [18]

All prepared formulations were evaluated for gelling capacity and viscosity in order to identify the compositions suitable for use as in situ gelling systems. The gelling capacity was determined by placing a drop of the system in a vial containing 2 ml of artificial tear fluid freshly prepared and equilibrated at 37^0C and visually assessing the gel formation and noting the time for gelation and the time taken for the gel formed to dissolve. The composition of artificial tear fluid used was sodium chloride 0.670 g, sodium bicarbonate 0.200 g, calcium chloride $2H_2O$ 0.008 g, purified water Q.S. 100.0 g. The viscosity was measured using a Brookfield Synchrolectric viscometer (RVT model) in the small volume adapter.

The viscosity measured at 20 rpm was used for purposes of comparative evaluation.

E. Rheological Studies [18]

Viscosity of instilled formulation is an important factor in determining residence time of drug in the eye. The developed formulations were poured into the small sample adaptor of the Brookfield Synchrolectric viscometer and the angular velocity increased gradually from 0.5 to 50 rpm. The hierarchy of the angular velocity was reversed. The average of the two readings was used to calculate the viscosity.

F. In vitro Release Studies [19]

The in vitro release of Gatifloxacin Hydrochloride from the formulations was studied through cellophane membrane using a modified USP XXIII dissolution testing apparatus. The dissolution medium used was artificial tear fluid freshly prepared (pH 7.4). Cellophane membrane, previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder (open at both ends and of 5 cm diameter). A 1ml volume of the formulation was accurately pipetted into this assembly. The cylinder was attached to the metallic driveshaft and suspended in 50 ml of dissolution medium maintained at 37± 1°C so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at 50 rpm using magnetic stirrer. Aliquots, each of 1ml volume, were withdrawn at hourly intervals and replaced by an equal volume of the receptor medium. The aliquots were diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 290 nm.

RESULTS AND DISCUSSION

A. Appearance

Clarity of all the formulations was found to be satisfactory. Terminal sterilization by autoclaving had no effect on the clarity and other physicochemical properties of the formulations. The haziness that was observed after autoclaving (due to precipitation of HPMC at elevated temperature) was found to disappear and the original clarity was regained after overnight standing.

B. pH

The pH of the formulations was found to be satisfactory and was in the range of 6-7.4. The formulations were liquid at room temperature and at the pH formulated. Terminal sterilization by autoclaving had no effect on the pH.

C. Drug Content

Table 2 shows the percent drug content for formulations MF 1, MF 2 and MF 3. The drug content was found to be in acceptable range for all the formulations. Percent drug content of formulations MF 1, MF 2 and MF 3 was found to be 97.88%, 98.46% and 99.24% respectively, indicating uniform distribution of drug.

Table 2: Drug content of the formulations

Formulation	% Drug content
MF 1	97.88%
MF 2	98.476%
MF 3	99.24%

D. In-vitro Gelation Studies and Viscosity

The two main prerequisites of an in situ gelling system are viscosity and gelling capacity (speed and extent of gelation). In case of Polyox and poloxamer based hydrogels, the viscosity increased in proportion with viscofying agent both at lower and higher concentration of gelling agent, i.e. gelling agent had a little effect on viscosity. While in case of sodium alginate based hydrogel, the viscosity increased in proportion with viscofying agent but gelling agent had more effect on viscosity than viscofying agent. This may be attributed to the higher viscosity of sodium alginate than other two gelling agents. On the basis of gelling capacity and viscosity, formulations MF 1, MF 2 and MF 3showed optimum results within the desired range.

E. Rheological Studies

Table 3 shows the viscosity values obtained for formulations MF 1, MF 2 and MF 3 using Brookfield DV-111+ rheomoter at different angular velocity. Formulations were shear thinning and an increase in shear stress was observed with increase in angular velocity (pseudoplastic rheology). The results obtained from the rheological study of prepared in situ gelling system MF 1, MF 2 and MF 3 revealed that the viscosity decreases as the angular velocity increases. Generally viscosity values in the range of 15-50 cps significantly improve the contact time in the eye. Higher viscosity values offer no significant advantage and have a tendency to leave a noticeable residue on the lid margin. The rheological profile of prepared in situ gelling systems of Gatifloxacin Hydrochloride is shown in Figure 1.

Table 3 : Rheological profile of the In-situ gelling systems

		Viscosity (x 100 cP)		
Sr.no.	Angular Velocity (rpm)	MF 1	MF 2	MF 3
1	0.5	88.145	90.824	89.453
2	1.5	74.362	77.231	72.321
3	2.5	61.773	65.740	60.324
4	5	42.722	43.692	40.273
5	10	27.915	28.464	26.472
6	20	15.724	16.108	15.213
7	30	12.731	13.947	12.642
8	40	11.749	12.155	11.113
9	50	11.148	11.154	10.873

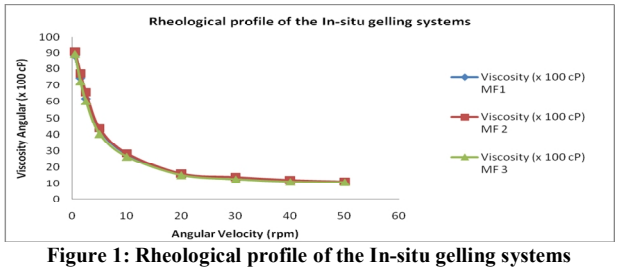

Figure 1: Rheological profile of the In-situ gelling systems

F. In Vitro Release Studies

The three in situ gelling formulations of Gatiifloxacin Hydrochloride, MF 1, MF 2 and MF 3, were subjected to in vitro release studies. These in vitro release studies were carried out using simulated tear fluid (STF) of pH 7.4 as the dissolution medium. The drug release data obtained for formulations MF 1, MF 2 and MF 3 is tabulated in Table 5. Figure 3 shows the plot of cumulative percent drug released as a function of time for formulation MF 1, MF 2 and MF 3. It was found that cumulative percent drug release was 77.34%, 75.84% and 71.38% for formulation MF 1, MF 2 and MF 3 respectively after 8 hours. The vitro release data indicated that the formulation MF 3 showed better sustained effect than other two formulations.

Table 4: Absorbance of different concentration of standard solution

Sr.no.	Concentration	Absorbance
1	2	0.0978
2	4	0.165
3	6	0.256
4	8	0.342
5	10	0.422
6	12	0.521
7	14	0.646

Table 5: In Vitro Drug Release Profile of Gatifloxacin Hydrochloride

Time	% Cumulative drug release (MHF 1)	% Cumulative drug release (MHF2)	% Cumulative drug release (MHF3)
1	30.14	29.78	28.11
2	36.83	35.28	34.13
3	42.68	42.90	39.59
4	49.95	48.71	44.43
5	55.37	53.72	51.12
6	63.54	62.48	57.38
7	69.89	69.25	63.71
8	77.34	75.84	71.38

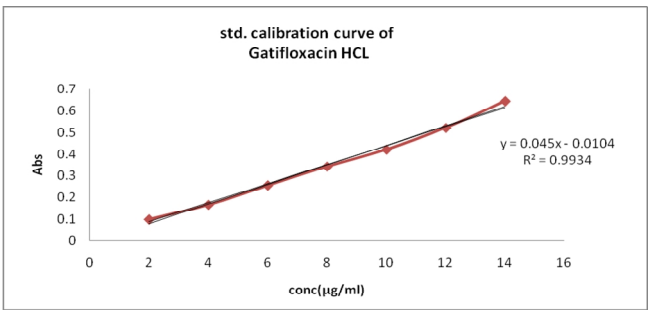

Figure 2: Standard calibration curve of Gatifloxacin HCL

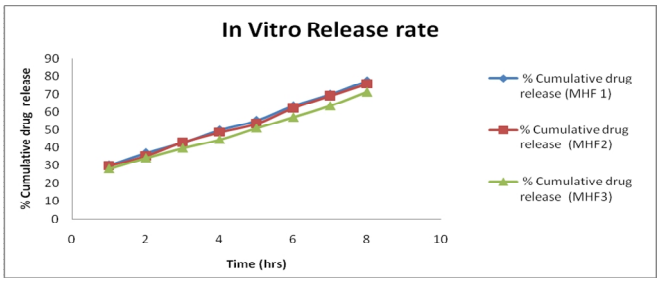

Figure 3: In Vitro Drug Release Profile of Gatifloxacin Hydrochloride

CONCLUSION

The primary requirement of a successful controlled release product focuses on increasing patient compliance which the in situ gels offer. The formulation (MF3) containing HPMC (K4M) and Poloxamer as polymer satisfied required pharmaceutical characteristics of hydrogels and was found promising. Formulation MF3 showed most sustained drug release. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the hydro gels dosage forms very reliable. As ocular efficiency of topically applied drugs is influenced by the corneal contact time, most common method of improving ocular availability of drugs is to increase precorneal residence time by using hydrogels.

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